Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age

Background paper for SAGE discussions

SAGE non-specific effects of vaccines Working Group

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A. EPIDEMIOLOGY REVIEW CONCLUSIONS AND RECOMMENDATIONS[1]

Preamble

The Working Group members noted the important impact of the vaccines under review on morbidity and mortality worldwide and their documented contribution to the reduction in the burden of the target diseases in all settings.

In addition, the Working Group members emphasised that the aim of their review was not to assess whether or not the vaccines should continue to be recommended for universal use, but to evaluate if there was evidence that the timing, sequence or co-administration of these vaccines could result in non-specific effects (beneficial or deleterious) on all-cause mortality.

The overall evidence base for effects of specific vaccines on all-cause mortality is not strong. Very large studies are required to study this in most populations, most studies would have insufficient statistical power to address this mortality question and, it is therefore reasonable to study such effects in settings of high mortality where a given relative effect should be more easily detectable. The collection of data on all the factors associated with mortality is often difficult in such settings thus limiting the ability to draw inferences from such studies, especially from observational rather than randomized studies.

The epidemiology review report does not include summary estimates from meta-analyses because there was consensus during the face-to-face meeting that it was not valid in this instance for the following reasons.

The Cochrane Handbook for Systematic Reviews stipulates that that the use of single summary statistics from non-randomised studies should be discouraged. Another central issue is that sampling error can be very much smaller than uncertainties due to bias, selection, missing data, reporting so that even the use of 99% confidence intervals could be misleading.

In addition to issues of statistical heterogeneity, and different levels of target diseases between populations (thus different specific-effect contributions to all-cause mortality), there is another fundamental reason to question the appropriateness of meta-analysis in this context. The hypothesis of non-specific effects implies protection against “other causes of mortality” than a vaccine’s target disease. We do not know what these may be, precisely, but it is not unreasonable to suppose that they be different – and/or be present to different degrees or frequencies - in different populations. We should thus expect, *a priori*, that non-specific effects would be heterogeneous, and differ considerably between populations. This expectation fits the data to date. It has repeatedly been pointed out that much of the evidence to date comes from specific poor West African populations with high child mortality risks - risks which probably reflect particular infection conditions of these populations.

[1] Higgins JPT, Soares-Weiser K and Reingold A. Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines, Report to WHO, 13 March 2013 (unpublished)

IS THE CURRENT EVIDENCE ON NON-SPECIFIC EFFECTS OF VACCINES SUFFICIENT TO LEAD TO ADJUSTMENTS IN POLICY RECOMMENDATIONS?

1. BCG VACCINE

Two randomized trials, three quasi-randomized trials, 12 cohort studies and one case-control study provided data on comparisons of BCG with no BCG in the neonatal period. Two out of the 5 included randomized/quasi randomised studies and 6 out of the 13 observational studies were conducted including investigators from the Guinea Bissau team.

Table 1. Studies eligible for BCG comparisons by judgement of risk of bias and by type of study design

Comparison	Risk of bias	Types of studies(*)		Total
		Randomized/ quasi randomised	Observational	
BCG vs. no BCG	Low	2 (2)		2(2)
	Moderate	3		3
	High		9 (6)	9(6)
	Very high		4	4
BCG vs. no BCG Boys and girls separately	Low	1 (1)		1(1)
	Moderate			
	High		6 (4)	6(4)
	Very high		2	2
BCG vs. no BCG Age of vaccination**	Low			
	Moderate			
	High		2 (2)	2(2)
	Very high			
BCG vs. no BCG Vitamin A supplementation	Low			
	Moderate			
	High		2 (1)	2(1)
	Very high			

(*) Studies assumed to have been conducted / analysed by the Guinea Bissau team.

** Results are also presented for different follow up times (1 observational study) and different age of first visit (1 observational study from Guinea Bissau)

Main conclusions

Overall, the Working Group found that the data from randomized studies and observational studies are suggestive of a beneficial effect of BCG in reducing all-cause mortality within the first 6-12 months of life in countries with high childhood mortality. There is no evidence of a deleterious effect of BCG on all-cause mortality.

The randomized and quasi-randomized trials all pointed towards a beneficial effect of BCG on overall mortality although none provided a conclusive result. The results of the nine non-randomized studies judged to have slightly lesser methodological concerns also indicated a beneficial effect of BCG on overall mortality within the first 6-12 months of life. Three studies with results with confidence intervals that excluded the 'no effect' line, each reported a positive effect of BCG. Estimated effects are in the region of a halving of mortality risk.

The available studies typically provided data on all-cause mortality, and did not allow examination of the 'non-specific effects' of BCG vaccine on deaths from causes other than tuberculosis. However, deaths from tuberculosis are infrequent in infants and young children, so any major effect of BCG vaccine on all-cause mortality is not likely to be attributable to a specific effect of BCG vaccine against tuberculosis.

The results of the epidemiology review did not provide evidence of a differential effect of BCG on all-cause mortality between boys and girls. Data reviewed did not provide evidence of an association between observed effects on mortality and age of vaccination. There was no evidence of a modifying effect of administration of vitamin A (prior or concurrent) on BCG effects.

These findings should be interpreted with caution. While two of the 5 trials were considered to be at low risk of bias, 3 were considered to be at moderate risk of bias. Of the observational studies, all were judged either as high risk of bias or as very high risk of bias. The GRADE rating (excluding those assessed to be at very high risk of bias) was of low confidence.

Important issues raised

- Although a reduction in all-cause mortality was noted in multiple studies, the Working Group members observed that the data available do not permit an unqualified inference that the observed benefits were non-specific, as the specific cause of death was not documented in all studies (e.g., whether specific clinical syndromes were reduced as opposed to all cause deaths). However, Working Group members commented that current understanding of the epidemiology of tuberculosis mortality in children seems inconsistent with this effect in 6-12 month olds being specific to BCG (i.e. TB).
- Current data are only available from high childhood mortality settings.
- There is evidence of BCG protective effects against leprosy (noting that *mycobacterium bovis* and *mycobacterium leprae* share a number of common antigens), and in the treatment of bladder cancer.
- It was noted that baseline confounding could tend to lead to bias towards a beneficial effect of the vaccine, because children with a worse prognosis generally tended to be vaccinated later or not vaccinated at all. However, it was also noted that it is not possible to establish with certainty the direction of such a bias unless there are data on who is vaccinated or not vaccinated by their prognosis. This may well vary from place to place and from time to time.
- The Working Group noted that in order to fully understand the public health relevance of these findings, one would wish to know the attributable protection or risk i.e., how many deaths or what proportion of deaths might actually be prevented in a given population, with a particular vaccine and schedule, if the "non-specific" effects were real.

Recommendations for SAGE´s consideration

The Working Group concluded that the evidence does not support a change in policy for BCG.

Additional lives might be saved by emphasizing the implementation of the WHO recommendation that a single dose of BCG be given to neonates or as soon as possible after birth in countries with a high prevalence of tuberculosis.

The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality in children.

2. DTP-CONTAINING VACCINES

Sixteen cohort studies and one case-control study were identified that provided comparisons of DTP with no DTP. There were no randomised controlled trials. All these studies were with whole cell pertussis vaccines. Seven out of the 16 studies were conducted in Guinea Bissau or included investigators from the Guinea Bissau team.

Table 2. Studies eligible for DPT comparisons by judgement of risk of bias and by type of study design

Comparison	Risk of bias	Types of studies (*)		
		Randomized/ quasi randomised	Observational	Total
DTP vs. no DTP	Low			
	Moderate			
	High		10 (6)	10(6)
	Very high		6 (1)	6(1)
DTP vs. no DTP Boys and girls separately	Low			
	Moderate			
	High		9 (6)	9(6)
	Very high		3 (1)	3(1)
DTP vs. no DTP Different ages of follow up**	Low			
	Moderate			
	High		4 (2)	4(2)
	Very high			
DTP vs. no DTP Vitamin A supplementation	Low			
	Moderate			
	High		1	1
	Very high			
BCG+DTP vs. BCG before DTP	Low			
	Moderate			
	High		3 (3)	3(3)
	Very high			
DTP before BCG vs. BCG before DTP	Low			
	Moderate			
	High		4 (3)	4(39
	Very high			
DTP + Measles vs. DTP before Measles	Low			
	Moderate			
	High		5 (5)	5(5)
	Very high			
DTP after Measles vs. DTP before Measles	Low			
	Moderate			
	High		3 (3)	3(3)
	Very high			

(*) Studies assumed to have been conducted / analysed by the Guinea Bissau team.

**No studies reported age of vaccination and two observational studies from Guinea Bissau reported results by age of the child the time they were seen

Main conclusions

The Working Group found mortality data related to DTP only from observational studies, and only when DTP was given in combination with other vaccines. These studies had significant methodological limitations. Because of these limitations, the overall effects of DTP vaccines under different epidemiological conditions remain unclear, in particular under circumstances where the burden of target diseases has been reduced to very low levels.[2]

[2] This conclusion was adjusted and finalized on June 6, 2014 (after the SAGE meeting of April 2014).

Most of the studies were carried out in populations where pertussis-containing vaccines have been in use for decades, and thus where pertussis circulation (as well as tetanus and diphtheria incidence) may have been substantially reduced.

The results of the 10 studies judged as having slightly lesser methodological concerns produced diverse results, ranging from a halving of mortality risk after DTP administration to a four-fold increase in mortality risk after DTP administration. The majority of studies indicated a negative effect of DTP. Three of the studies had 95% confidence intervals that excluded no effect. These were all undertaken in Guinea-Bissau. Four of the other results were from the same investigators of the Guinea-Bissau studies, three of which were re-analyses of studies undertaken by other teams. Two of these suggested possible negative effects and one had a 95% confidence interval favouring a positive effect of DTP. The three studies from different investigator teams produced more equivocal results.

The Working Group members differed in their interpretation of the inconsistent results. In the opinion of one member, the results are influenced by the fact that the reviewers included studies showing a beneficial effect of DTP that in the member's view had severe methodological problems and should not have been included in the review.

The results of the epidemiology review did not provide conclusive evidence of a differential gender effect of DTP containing vaccines on all-cause mortality. The available data did not permit meaningful examination of differences in the effect of DTP according to age at administration.

OPV was administered concomitantly with DTP in most included studies; two studies did not report OPV co-administration. It was not possible to separate any possible effects of DTP from OPV in the available studies.

Three observational studies provided data for the comparison of DTP given before BCG compared with DTP after BCG. A fourth observational study reported on DTP vaccine given before or with BCG versus DTP after BCG. No clear differences are apparent and the available data were insufficient to draw conclusions.

One cohort study reported that there was no evidence of a difference in effect of DTP according to vitamin A status.

These findings should be interpreted with caution as the data were obtained from observational studies judged to be at high or very high risk of bias and the majority were from the same setting. The GRADE rating (excluding those assessed to be at very high risk of bias) was of low confidence.

Important issues raised

- Concern was expressed about the representativeness, replicability and generalizability of data generated from a limited number of geographic settings and from one group of investigators.
- OPV was often co-administered with DTP (with the exception of two studies where the information was not available), leading to complete confounding of any possible effects of DTP alone.
- The ascertainment of cause of death is very weak in general, even in the presence of careful post mortems and verbal autopsies. The prevalence of various diseases (and of fatal disease) differs between populations, in some places being very low.
- The working group noted that age effects are important and complicated and were not considered fully in all publications. Background mortality patterns differ between populations and age may confound or interact with vaccines in different ways. Because the period post-DTP could be at different ages depending on when the child was vaccinated, analysis of mortality in the post-DTP period without consideration of age could bias an apparent effect of DTP on mortality.
- Study biases of several types (alone or together) can readily distort an effect in a range up to relative risk = 2 and possibly higher. Therefore extreme caution is required in drawing firm conclusions in the presence of known or suspected bias for relative risk <2. For relative risk >2, bias may still affect the point estimate, but the direction of effect is less likely to be falsely concluded, even if the estimate itself is uncertain.

- It was noted that baseline confounding could tend to lead to bias towards a beneficial effect of the vaccine, because children with a worse prognosis generally tended to be vaccinated later or not vaccinated at all (described as "frailty bias"). However, it was also noted that it is not possible to establish with certainty the direction of such a bias unless there are data on who is vaccinated or not vaccinated by their prognosis. This may well vary from place to place and from time to time.
- Although the Working Group members were interested in an assessment of the directionality of overall bias, the reviewers stated that given all the various sources of bias and confounding that could not be accounted for in the various studies "*we did not predict the direction of bias for individual studies or for the accumulated body of evidence*" (see section 10.1 ***Closing remarks on risk of bias*** and Annex C of the epidemiology review)

Recommendations for SAGE´s consideration

The Working Group concluded that the evidence does not support a change in policy for DTP.

The current WHO policy recommends three DTP doses during the first year of life. In areas where pertussis is of particular risk to young infants, DTP should be started at 6 weeks with two subsequent doses at intervals of 4-8 weeks each.

The data available do not provide conclusive evidence that the current schedule results in deleterious effects on all-cause mortality in children less than five years of age. Any findings should be interpreted with caution in light of the assessment of risk of bias.

3. MEASLES CONTAINING VACCINES

Four randomized trials, 22 cohort studies and two case-control studies were identified that provided comparisons of measles vaccine with no measles vaccine. Three out of the 4 randomized trials, 12 out of the 24 observational studies were either conducted in Guinea Bissau or included researchers from the Guinea Bissau team.

Table 3. Studies eligible for measles vaccine comparisons by judgement of risk of bias and by type of study design

Comparison	Risk of bias	Types of studies (*)		
		Randomized/ quasi randomised	Observational	Total
Measles vs. no measles	Low	4 (3)		4(3)
	Moderate			
	High		18 (11)+	18(11)
	Very high		6	6
Measles vs. no measles Boys and girls separately	Low	2 (2)		
	Moderate			
	High		6 (6)	6(6)
	Very high		3	3
Measles vs. no measles Age of follow up[3]	Low			
	Moderate			
	High		9 (4)	9(4)
	Very high			
Measles vs. no measles Vitamin A supplementation	Low			
	Moderate			
	High		3 (3)	3(3)
	Very high			

(*) Studies assumed to have been conducted / analysed by the Guinea Bissau team.
+ Assuming that three out of four studies from Senegal were analysed by the Guinea Bissau investigators.

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[3] one observational study reported age of vaccination, and another (from GB) reported different ages at first visit

Main conclusions

Overall, the Working Group found that there was evidence that measles vaccine reduced the risk of all-cause mortality independent of its effect on confirmed measles mortality (an effect that appears to be stronger in girls than boys).

Regarding the randomised trials, the reviewers noted that the number of deaths was low and the follow-up period short and therefore the findings were inconclusive.

Results from these trials pointed towards a beneficial effect of measles vaccine. The results from 18 non-randomised studies judged to be at high risk of bias consistently observed effects similar to those reported in the randomised trials. Estimated effects are in the region of halving the mortality risk.

Data from 9 cohort studies and two randomised trials provided comparisons of measles vaccine with no measles vaccine separately for boys and girls. Effects of the vaccine in girls appear to be more beneficial than in boys in 3 studies and the other studies found no convincing evidence in either direction.

There were no consistent findings regarding a difference in effect of measles vaccine according to vitamin A status.

These findings should be interpreted with caution as the data were obtained from randomised trials judged to be at low risk of bias and from observational studies judged to be at high or very high risk of bias. The GRADE rating (excluding those assessed to be at very high risk of bias) was of low confidence.

Important issues raised

- The Working Group noted that more weight could be given to the results from randomized studies than data from observational studies. It was noted that that data from most non-randomised studies also suggested a beneficial effect of measles vaccine.
- Members also noted that while the results of the randomized studies suggested a beneficial effect, the 95% confidence intervals included zero. It was noted that baseline confounding could tend to lead to bias towards a beneficial effect of the vaccine, because children with a worse prognosis for survival generally tend to be vaccinated later or not vaccinated at all. However, it was also noted that it is not possible to establish with certainty the direction of bias unless there are data on who is vaccinated or not vaccinated by their prognosis. This may well vary from place to place and from time to time.
- Although the Working Group members were interested in an assessment of the directionality of the bias, the reviewers stated that given all considerations to the various sources of bias and confounding that could not be accounted for in the studies included “we did not predict the direction of bias for individual studies or for the accumulated body of evidence” (see section 10.1 **Closing remarks on risk of bias** and Annex C of the epidemiology review).
- The Working Group noted that the size of the effect on all cause-mortality in some studies was large, and that the size of the observed effects on mortality reductions appeared too large to be explained by the prevention of measles deaths alone.
- In populations with very high coverage of measles vaccine, deaths from measles should be infrequent. One Working Group member argued that the results from 10 studies where measles deaths had been removed or censored suggest that these effects were not fully explained by deaths that were established as due to measles.
- However, it was noted that we do not know causes of most deaths and some members argued that the mortality reduction was most likely to be a specific effect.
- The Working Group considered the proposal for current recommendations regarding giving measles containing vaccines at older ages (i.e. during the second year of life or later) should be further assessed in light of the possibility of administering measles vaccine earlier in life to maximize protection from non-measles causes of death. However, it was noted that the current challenges for measles control include vaccine failure (antibody response has been documented to be lower when the vaccine is administered at younger ages) and failure to vaccinate (coverage is insufficient to induce high levels of population immunity). Some members noted that most women of reproductive age now have developed measles immunity from immunization rather than from natural infection. It

has been reported that children born to these women have lower levels of antibodies/or that their antibody levels decline at a younger age, thus making interference of measles vaccine with maternally derived antibodies less of an issue for measles vaccine at early ages.

- Some Working Group members raised concerns about drawing conclusions from these studies to recommend lowering the age of measles immunization without further studies of earlier age dosing effects on measles-specific immune responses and on secondary vaccine failure in the targeted populations. There are substantial data that immaturity of the immune system decreases seroconversion in a manner that is distinct from the effect of maternal antibody, and that immunization at later ages provides better protection from reinfection.
- It was also noted that the studies were conducted in settings where wild type measles virus circulation is endemic.

Recommendation for SAGE´s consideration

The Working Group concluded that the evidence does not support a change in policy for measles vaccine

The current WHO recommendation states that reaching all children with 2 doses of measles containing vaccine should be the standard for all national immunization programmes. In countries with ongoing transmission, measles containing vaccine should be given at age 9 months. WHO recommends that the second dose should be given between 15-18 months of age. In countries with low rates of measles transmission, the first dose may be administered at age 12 months.

The available data suggest that the current WHO recommended schedule for standard titre measles-containing vaccine has a beneficial effect on all-cause mortality in children.

Additional lives might be saved by improving implementation of the WHO recommendation.

B. IMMUNOLOGY REVIEW CONCLUSIONS AND RECOMMENDATIONS

IS THE CURRENT EVIDENCE ON NON-SPECIFIC EFFECTS OF VACCINES SUFFICIENT TO LEAD TO ADJUSTMENTS IN POLICY RECOMMENDATIONS?

Main conclusions

Overall, the Working Group determined that the findings from the systematic review neither excludes nor confirms the possibility of beneficial or deleterious non-specific immunological effects of vaccines on all cause-mortality.

There is substantial heterogeneity of study designs and immunological parameters studied, and consequently it is difficult to meaningfully summarise the data.

Furthermore, although it is recognised that there are nonspecific immunological effects, the currently available data from the literature on human studies do not provide consistent findings to confirm or refute the presence of non-specific immunological effects in humans following vaccination with BCG, diphtheria, pertussis, tetanus or measles containing vaccines.

There is no evidence from the human literature as to whether it is plausible or not that vaccines can cause the putative nonspecific effects on mortality that have been observed in some epidemiological studies.

While nonspecific effects are clearly described in animal studies, the human data do not provide the necessary evidence to provide clinical relevance or any confidence in the quality, quantity, kinetics or impact of non-specific immunological effects in young children after vaccination. Importantly, any findings regarding changes in the studied immunological parameters cannot be linked to any relevant clinical endpoints used to measure non-specific effects in human subjects.

Important issues raised

- The biological mechanisms underlying any non-specific immunological effects following vaccination and its relationship to all-cause mortality in infants are not well defined and more research in this area is needed. This presumes that the immunological markers or biomarkers for effect on the mortality pathway are clear.
- There is no evidence to link specific changes in immunological markers with mortality in humans.
- There are no robust data to characterize consistent non-specific immunological effects following vaccination in infants.
- Some members of the Working Group posed the question as to whether it is it biologically plausible to see the magnitude of effects that are being hypothesized in some of the epidemiological studies (e.g. 30% increase or decrease in mortality), given the lack of coherence or signal in the immunological studies.
- Other members were of the opinion that while there are no immunological markers for the “specific” effect of BCG it could not be asserted that it is biologically implausible that BCG reduces miliary TB, TB meningitis and leprosy.

Recommendation for SAGE´s consideration

The available evidence is insufficient to draw any conclusions on non-specific immunological effects following vaccination that would provide the biological basis for non-specific effects on all-cause mortality.

There was agreement that non-specific immunological effects following exposure to any antigen are plausible and common but their biologic effects are not clearly understood in general and, specifically for vaccines. This should include immunological studies to examine issues such as gender as well as, as vaccine sequence and/or combinations of vaccines which are of potential relevance and other issues such as gender and age.

C. RESEARCH AGENDA

There was insufficient time for the Working Group to fully explore future research directions arising from this review.

Nevertheless, some broad principles emerged during the review. As a preliminary guide for SAGE discussion, the following observations were made.

The SAGE-commissioned review was tightly constrained to focus on mortality only. Broader considerations of morbidity in human population studies (with embedded immunologic investigation that will inform putative effect determination and underlying mechanisms) should form part of future research considerations.

There is a need for more high quality randomised controlled trials, wherever feasible.

There are ethical and methodologic challenges facing sufficiently powered population studies of mortality, particularly with respect to DTP vaccine. Randomised controlled trials of any DTP versus no DTP, even with narrow time windows for outcome evaluation, and even in settings where endemic pertussis is low, may not be able to be conducted. The widespread use of pentavalent vaccine further complicates examination of putative specific vaccine effects

If additional RCTs were to be conducted, it may be appropriate to aim for several large studies across a number of countries using the same protocol. Randomised controlled trials of EPI schedule variants designed to minimise post-vaccination DTP person-time exposure before MCV vaccine could be considered.

Any future studies should be designed and powered to examine gender effects. In addition, immunological analysis should become a specific objective of future studies based on formulating specific research questions that the study could answer. This could include assays that cover a breadth of immunological responses including antibodies, T-cell responses, cytokines, etc. However, the Working Group argued against a shotgun approach given that it would make interpretation of occasionally significant results among hundreds of comparisons difficult. Systems biology approaches may be particularly informative in providing a profile of host immune response.

There was a view that further observational studies with inherent and substantial risk of bias would be unlikely to provide conclusive evidence about putative non-specific mortality effects. However, if observational studies are to be contemplated, their design and analysis should mimic what would be undertaken if it were to be a randomised controlled trial.

Future studies should draw upon a broad investigator pool and from a wide range of geographic locations and burden of disease settings.

The development of standardized protocols for both RCTs and observational studies of mortality effects, that address now well-recognised bias issues, should be considered.